REMARKS

Claims 48-152 are pending in the application. Claims 100-152 are withdrawn, as discussed in greater detail below. Claims 48, 50-51, 55-75, 81, 84-94, and 97-98 stand rejected under 35 U.S.C. § 102(b) over WO90/15070 ("Pirrung"). Claims 49, 52-54, 76-77, 79-80, 82, 83, 96, and 99 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of WO 89/10977 ("Southern") and US 4,877,745 ("Hayes") and US 4,937,593 ("Prats"). Claims 76, 78, and 95 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of US 3,615,240 ("Sanz") and US 5,306,510 ("Meltzer"). Applicants respectfully traverse all rejections.

I. Restriction

The Examiner is requiring Applicants to restrict prosecution between the invention of Group I (claims 48-99), which are directed to a method of forming an array of polymers on a support having one or more localized areas and the invention of Group II (claims 100-152), which are directed to an automated apparatus for forming an array of polymers on a support having one or more localized areas. Applicants respectfully traverse the restriction requirement. However to advance prosecution of this case, Applicants elect Group I (claims 48-99).

II. The Objection to the Disclosure Is Overcome

The disclosure is objected to for incorrectly indicating the priority status of the present application in the paragraph beginning at page 1 immediately following the title. Specifically, Applicants inadvertently and incorrectly indicated that 07/796,243, filed November 22, 1991 is a continuation-in-part of 07/874,849, filed April 24, 1992. Applicants have correctly indicated the priority status of the present application in the above amendment to the specification. The above

amendment to the specification further reflects the updated status of USSN 08/426,202 by indicating that it issued as U.S. Patent No. 6,136,269. Accordingly, the objection to the disclosure is overcome.

III. The Effective Priority Date Is November 22, 1991

The Examiner asserts that the instant claims have an effective filing date of 11/20/92 (the filing date of U.S. Patent Application No. 07/980,523, now U.S. Patent No. 5,677,195) because the teaching of a resist is supposedly not found in US Patent No. 5,384,261 filed November 22, 1991. Applicants respectfully traverse the Examiner's assertion.

Applicants submit that U.S. Patent Application No. 07/796,243, now U.S. Patent No. 5,384,261, filed November 22, 1991 does indeed provide support for a resist in the practice of the presently claimed method. Support for a resist can be found throughout U.S. Patent No. 5,384,261, for example at column 6, lines 50-57:

> Thereafter, a monomer B is coupled to second selected regions, some of which may be included among the first selected regions. The second selected regions will be in fluid contact with a second flow channel(s) through translation, rotation, or replacement of the channel block on the surface of the substrate; through opening or closing a selected valve; or through **deposition of a layer of photoresist**. (Emphasis added).

Additional support for a resist is found at column 8, lines 42-56:

> According to other embodiments the channels will be formed by depositing an electron or photoresist such as those used extensively in the semiconductor industry. Such materials include polymethyl methacrylate (PMMA) and its derivatives, and electron beam resists such as poly(olefin sulfones) and the like (more fully described in Ghandi, "VLSI Fabrication Principles," Wiley (1983) Chapter 10, incorporated herein by reference in its entirety for purposes). According to these embodiments, a resist is deposited, selectively exposed, and etched, leaving a portion of the substrate exposed for coupling. These steps of depositing resist, selectively removing resist and monomer coupling are repeated to form polymers of desired sequence at desired locations.

Surely, there is adequate support in U.S. Patent No. 5,384,261 for independent claims 48 and 97. In particular, U.S. Patent No. 5,384,261 discloses the steps of depositing a resist onto a surface of a support and selectively removing a portion of the resist to expose one or more localized areas. Further, support for all pending dependent claims can be found throughout U.S. Patent No. 5,384,261 in addition to those portions cited above. Thus, U.S. Patent No. 5,384,261 provides adequate support for the instant claims and Applicants respectfully request that the present application be granted priority to U.S. Patent No. 5,384,261, filed November 22, 1991.

IV. Claims 48, 50-51, 55-75, 81, 84-94, and 97-98 Are Patentable over Pirrung

Claims 48, 50-51, 55-75, 81, 84-94, and 97-98 stand rejected under 35 U.S.C. § 102(b) over Pirrung. Applicants respectfully traverse this rejection.

Independent claims 48 and 97 are patentable over Pirrung at least because Pirrung fails to disclose, either explicitly or inherently, the claimed steps of depositing a resist on the surface of a support and selectively removing a portion of the resist to expose one or more localized areas. The Examiner asserts at page 4 of the present Office Action that the protected species layers constitute the instant "resist" in that they are resistant to chemical reaction. However, the protective groups used in the masking strategy disclosed in Pirrung are labile groups bound to a monomer unit on the surface of the support. For example, Pirrung defines the protective groups at page 13, line 33 – page 14, line 7:

> Protective Group: A **material which is bound to a monomer unit and which may be spatially removed upon selective exposure to an activator** such as electromagnetic radiation. Examples of protective groups with utility herein include Nitroveratryloxy carbonyl, Nitrobenzyloxy carbonyl, Dimethyl dimethoxybenzyloxy carbonyl, 5-Bromo-7-nitroindolinyl, o-Hydroxyl-α-methyl cinnamoyl, and 2-oxymethylene anthraquinone. Other examples of activators include ion beams, electric fields, magnetic fields, electron beams, x-ray, and the like. (Emphasis added).

In contrast, the resist of the present invention described at page 20, lines 1-9 is not a labile group bound to a monomer – it is deposited on a surface of the support:

> In some embodiments, a resist can be used to activate certain regions of the substrate. Certain resist materials such as acid-generating polymers, for example, will release protons upon irradiation. According to these embodiments, a substrate covered with such material [*ed: a resist*] is irradiated through a mask or otherwise selectively irradiated so that the irradiated regions of the substrate are exposed to acidic conditions. Acid-labile protecting group on the substrate or oligomers on the substrate are removed, leaving an activated region.

Thus, the presently claimed resist is patentably distinguishable from Pirrung's protective groups for at least this reason.

It is noted that a practical difference between the method disclosed by Pirrung and the presently claimed method can be appreciated from Applicants' disclosure at page 20, lines 1-9 (quoted above). From this portion of the application, it is apparent that a resist generates acid upon irradiation which cleaves the protecting groups from the monomers in these embodiments. In contrast, Pirrung generally discloses removing protecting groups via photolithographic means. Further, nowhere does Pirrung disclose, either explicitly or inherently, that Pirrung's protective groups can generate acid upon irradiation. In this regard, the presently claimed resists contemplate both positive resists (i.e., resists that degrade and become more easy to remove upon irradiation) and negative resists (i.e., resists that become more durable upon exposure to radiation). See "VLSI Fabrication Principles" by Ghandhi at p. 557, which is incorporated in the application by reference. Nowhere does Pirrung disclose, explicitly or inherently, removing such protecting groups using a resist.

Accordingly, nowhere does Pirrung disclose, explicitly or inherently, depositing a resist on the surface of a support and selectively removing a portion of the resist to expose one or more localized areas, as defined by independent claims 48 and 97. As such, dependent claims 49-96

and 98-99 are patentable over Pirrung at least by virtue of their dependency. Thus, removal of the present rejection is respectfully requested at this time.

V. Claims 49, 52-54, 76-77, 79-80, 82, 83, 96, and 99 Are Patentable over Pirrung in View of Southern, Hayes, and Prats

Claims 49, 52-54, 76-77, 79-80, 82, 83, 96, and 99 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of Southern, Hayes, and Prats. Applicants respectfully traverse this rejection in view of the following remarks.

Independent claims 48 and 97 are patentable over Pirrung in view of Southern, Hayes, and Prats at least because none of the presently cited references, either alone or in combination, disclose or otherwise teach or suggest the claimed steps of depositing a resist on the surface of a support and selectively removing a portion of the resist to expose one or more localized areas. As discussed in detail above, Pirrung fails to disclose or otherwise teach or suggest a resist because the protective groups of Pirrung are patentably distinguishable from the resist defined by claims 48 and 97.

All other presently cited references fail to cure the deficiencies of Pirrung. Southern fails to teach or suggest the use of a resist. Also, Importantly, later publications by Southern demonstrate the problems Southern encountered in creating arrays of any sufficient density or sufficiently small cell size on the order presently claimed by applicants using his technology. (See for example claim 67 reciting a localized area of 100 μm^2 with claims 91 and 92 reciting densities of localized areas of 1000 and 10,000 per cm^2, respectively.) At page 1014, paragraph 5 of Southern et al. "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Array of Oligonucleotides: Evaluation Using Experimental Models", *Genomics* 13, 1008-1017 (1992), Southern discloses that "[a]n array of all octanucleotides would occupy an area 256 x

256 mm with a cell size of 1 mm^2, which is probably close to the limit of the method described here . . . ." For creating smaller arrays, Southern relies on the teachings of Fodor et al., "Light-directed, Spatially Addressable Parallel Chemical Synthesis," *Science*, 251:767-773 (1991):

> Printing methods with a resolution of 10 μm could be used to form masks resistant to the oligonucleotide precursors or the deprotecting agents. Photolithographic techniques can be used to remove photolabile blocking groups at each cycle of synthesis. (Fodor, et al., 1991). This method can produce cells down to a size of 25 μm. Such small cell sizes would produce a device 40-100 mm square for an array of all dodecamers, with the potential to analyze runs of around 4000 bases.

Id.

In a still later publication, Southern still is unable to use his methods to obtain an array of any sufficient density. "Our methods limit us to a cell size of less than 2 mm, whereas the photodeprotection method can give cells 50 μm square." Southern & Maskos, "Parallel Synthesis and Analysis of Large Number of Related Chemical Compounds: Applications to Oligonucleotides", *Journal of Biotechnology* 35 (1994) at page 221, paragraph 3. At page 225 of that same reference, Southern states that:

> the limit for our physical separation of channels is likely to be in the 1 mm range and is therefore sufficient for 8-mer arrays with an array size of approximately 25 cm x 25 cm. To decrease cell size further, a number of alternatives can be pursued.
>
> Photolithography (Fodor, et al., 1991) is one possibility to synthesize oligonucleotides in patches of down to 50 μm x 50 μm. The key parameter to be improved are stepwise yield, currently 80-95%, and the possibility to completely mask off areas of the plate that are not supposed to take part in any given deprotection step, which would otherwise result in failure sequences. This point is difficult to address given the relatively long deprotection times (of the order of 30 min) required.

Hayes and Prats also do not cure the deficiencies of Pirrung as Hayes relates to a process for reagent fluid dispensing and printing, and Prats relates to a print head position control system. Neither Hayes nor Prats even contemplates depositing a resist onto a surface of the

support or selectively removing a portion of the resist to expose one or more localized areas, as claimed by Applicants. Thus, for at least the reasons presented above, independent claims are patentable over Pirrung in view of Southern, Hayes, and Prats.

Since independent claims 48 and 97 are patentable over the above cited references, it follows that claims 49, 52-54, 76-77, 79-80, 82, 83, 96, and 99 are patentable over Pirrung in view of Southern, Hayes, and Prats at least by virtue of their direct or indirect dependency. Accordingly, removal of the present rejection is respectfully requested at this time.

VI. Claims 76, 78, and 95 Are Patentable over Pirrung in View of Sanz and Meltzer

Claims 76, 78, and 95 stand rejected under 35 U.S.C. § 103(a) over Pirrung in view of Sanz and Meltzer. Applicants respectfully traverse this rejection in view of the following remarks.

Independent claims 48 and 97 are patentable over Pirrung in view of Sanz and Meltzer because none of the references, either alone or in combination, disclose or otherwise teach or suggest the claimed steps of depositing a resist on the surface of a support and selectively removing a portion of the resist to expose one or more localized areas. As discussed in detail above, Pirrung fails to disclose or otherwise teach or suggest a resist because the protective groups of Pirrung are patentably distinguishable from the resist defined by claims 48 and 97.

All other presently cited references fail to cure the deficiencies of Pirrung. Sanz teaches a micropipette comprising a pawl mechanism for driving a rotary member. Meltzer teaches a liquid sample handling system. Nowhere does Sanz or Meltzer disclose or otherwise teach or suggest a resist as presently claimed. Accordingly, Sanz and Meltzer fails to disclose or otherwise teach or suggest the claimed steps of depositing a resist on the surface of a support and

selectively removing a portion of the resist to expose one or more localized areas. Thus, independent claims 48 and 97 are patentable over the presently cited references, either alone or in combination.

Since independent claims 48 and 97 are patentable over the above cited references, it follows that claims 76, 78, and 95 are patentable over Pirrung in view of Sanz and Meltzer at least by virtue of their direct or indirect dependency. Accordingly, removal of the present rejection is respectfully requested at this time.

VII. The Examiner's Request for an Information Disclosure Statement

The Examiner asserts that the Information Disclosure Statement filed March 12, 2002 is missing from the application file and is requesting a copy of the IDS filed March 12, 2002 for completeness of record. As of the date of the present Office Action, Applicants have not filed an IDS in the instant case. In response, Applicants are submitting herewith an Information Disclosure Statement for filing in the present case. The Examiner is urged to contact the undersigned if further assistance regarding this matter is desired.

VIII. Conclusion

Having addressed all outstanding issues, Applicants respectfully request reconsideration and allowance of all claims at this time. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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John P. Iwanicki, Reg. No. 34,628
BANNER & WITCOFF, LTD.
28 State Street, 28th Floor
Boston, MA 02109
(617) 720-9600